REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested. Pursuant to 37 CFR § 1.121, attached as Appendix A is a Version With Markings to Show Changes Made. Support for new claims 55-70 is found in original claims 11-19, 21-24, and 26-28, respectively, as well as the specification of the present application.

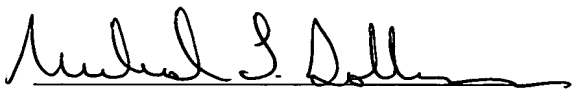
The rejection of claims 1-10 under 35 U.S.C. § 101 for double-patenting over U.S. Patent No. 6,027,889 to Barany et al. is respectfully traversed in view of the above amendments.

The rejection of claims 29-34 and 51-54 under 35 U.S.C. § 101 for double-patenting over U.S. Patent No. 6,268,148 to Barany et al. is respectfully traversed in view of the above amendments.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: December 17, 2002



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12/17/2002 Date	JoAnn Whalen

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~~Appendix A~~

Version With Markings to Show Changes Made

In reference to the amendments made herein to claims 1-10, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

In The Claims:

1. (Amended) A method for identifying one or more [of a plurality of sequences differing by one or more single-base changes, insertions, deletions, or translocations in a plurality of] different target nucleotide sequences comprising:

providing a sample potentially containing one or more target nucleotide sequences [with a plurality of] comprising sequence differences;

providing one or more oligonucleotide probe sets, each set [characterized by] comprising (a) a first oligonucleotide probe[, having] comprising a target-specific portion and a 5' upstream primer-specific portion and (b) a second oligonucleotide probe[, having] comprising a target-specific portion and a 3' downstream primer-specific portion, wherein the first and second oligonucleotide probes in [a] each particular set are suitable for ligation together when hybridized [adjacent to one another] on a corresponding target nucleotide sequence, but have a mismatch which interferes with such ligation when first and second oligonucleotide probes are hybridized to any other nucleotide sequence present in the sample;

providing a ligase;

blending the sample, the [plurality of] one or more oligonucleotide probe sets, and the ligase to form a ligase detection reaction mixture;

subjecting the ligase detection reaction mixture to one or more ligase detection reaction cycles [comprising a denaturation treatment, wherein any hybridized oligonucleotides are separated from the target nucleotide sequences, and a hybridization treatment, wherein the oligonucleotide probe sets hybridize at adjacent positions in a base-specific manner to their respective target nucleotide sequences, if present in the sample, and ligate to one another] to form a ligation product sequence [containing] comprising (a) the 5' upstream primer-specific portion, (b) the target-specific portions [connected together], and (c) the 3' downstream primer-specific portion [with the ligation product sequence for each set being distinguishable from other nucleic acids in the ligase detection reaction mixture, and, wherein the oligonucleotide probe sets may hybridize to nucleotide sequences in the sample other than their respective target nucleotide sequences but do not ligate together due to a

presence of one or more mismatches and individually separate during the denaturation treatment], when the respective target nucleotide sequence of the corresponding oligonucleotide probe set is present in the sample;

providing one or a plurality of oligonucleotide primer sets, each set [characterized by] comprising (a) an upstream primer containing the same sequence as the 5' upstream primer-specific portion of the ligation product sequence and (b) a downstream primer complementary to the 3' downstream primer-specific portion of the ligation product sequence[, wherein one of the primers has a detectable reporter label];

providing a polymerase;

blending the ligase detection reaction mixture with the one or a plurality of oligonucleotide primer sets, and the polymerase to form a polymerase chain reaction mixture;

subjecting the polymerase chain reaction mixture to one or more polymerase chain reaction cycles [comprising a denaturation treatment, wherein hybridized nucleic acid sequences are separated, a hybridization treatment, wherein the primers hybridize to their complementary primer-specific portions of the ligation product sequence, and an extension treatment, wherein the hybridized primers are extended to form extension products complementary to the sequences to which the primers are hybridized, wherein, in a first cycle, the downstream primer hybridizes to the 3' downstream primer-specific portion of the ligation product sequence and extends to form an extension product] to form extension products comprising the ligation product sequence and/or complements thereof [complementary to the ligation product sequence[, and, in subsequent cycles, the upstream primer hybridizes to the 5' upstream primer-specific portion of the extension product complementary to the ligation product sequence and the 3' downstream primer hybridizes to the 3' downstream portion of the ligation product sequence]; and

detecting the extension products to identify [reporter labels; and

distinguishing the extension products to indicate the presence of] one or more target nucleotide sequences in the sample.

2. (Amended) A method according to claim 1, wherein one of the oligonucleotide probes in [the] each set [contains] comprises a restriction site, said method further comprising:

restriction digesting each extension product at the restriction site[s] to produce [labelled] extension product fragments, wherein the restriction site is positioned in each of the oligonucleotide probe sets to produce an extension product fragment with a unique length so that it can be distinguished from other nucleic acids in the polymerase chain reaction mixture after said restriction digesting; and

separating the extension product fragments by size or electrophoretic mobility, wherein said [distinguishing] detecting differentiates the extension product fragments which differ in size.

3. (Amended) A method according to claim 1, wherein the ligation product sequence of the oligonucleotide probes in [a] each particular set produces an extension product of unique length [so that it can be distinguished from other nucleic acids in the polymerase chain reaction mixture], said method further comprising:

separating the extension products by size or electrophoretic mobility, wherein said [distinguishing] detecting differentiates the extension products which differ in size.

4. (Amended) A method according to claim 1, wherein the [oligonucleotides] oligonucleotide probes in each set are configured so that the sequence of [their] the ligation product[s across the ligation junction of each] sequence from each oligonucleotide probe set is unique and can be distinguished from other nucleic acids in the polymerase chain reaction mixture, said method further comprising:

providing a solid support with different capture oligonucleotides immobilized at different particular sites, wherein the capture oligonucleotides have nucleotide sequences complementary to the unique nucleotide sequences [across the ligation junctions] of given probe sets;

contacting the polymerase chain reaction mixture, after said subjecting it to one or more polymerase chain reaction cycles, with the solid support under conditions effective to hybridize the extension products to the capture oligonucleotides in a base-specific manner, [thereby capturing the extension products on the solid support at the site with the complementary capture oligonucleotide,] wherein said detecting indicates the presence of extension products captured using the unique nucleotide sequence portions [surrounding the

ligation junction and immobilized to the solid support at particular sites, thereby indicating the presence of] to identify one or more target nucleotide sequences in the sample.

5. (Amended) A method according to claim 1, wherein, in each primer set, one primer [has] comprises a detectable reporter label and the other primer [contains] comprises an addressable array-specific portion which is linked to the 5' end of that primer and remains single stranded after said subjecting the polymerase chain reaction mixture to one or more polymerase chain reaction cycles, said method further comprising:

providing a solid support with different capture oligonucleotides immobilized at different particular sites, wherein the capture oligonucleotides have nucleotide sequences complementary to the addressable array-specific portions;

contacting the polymerase chain reaction mixture, after said subjecting it to one or more polymerase chain reaction cycles, with the solid support under conditions effective to hybridize the extension products to the capture oligonucleotides in a base-specific manner[, thereby capturing the addressable array-specific portions to the solid support at the site with the complementary capture oligonucleotide], wherein said detecting indicates the presence of extension products captured [using the addressable array-specific portions and immobilized to the solid support] at particular sites[, thereby indicating the presence of] to identify one or more target nucleotide sequences in the sample.

6. (Amended) A method according to claim 1, wherein the relative amounts of two or more [of a plurality of] differing sequences[, differing by one or more single-base changes, insertions, deletions, or translocations and] are present in a sample in unknown amounts with a plurality of target nucleotide sequences being quantified and a set of oligonucleotide primers being useful in amplifying all the ligation product sequences formed by the oligonucleotide probe sets in [a] each particular probe group, the oligonucleotide probe sets forming a plurality of oligonucleotide probe groups, each group comprised of two or more of the oligonucleotide probe sets, wherein oligonucleotide probe sets in the same group [contain] comprise the same 5' upstream primer-specific portion and the same 3' downstream primer-specific portion, said method further comprising[;]:

quantifying the relative amount of the extension products, after said [distinguishing] detecting and

comparing relative amounts of the extension products generated to provide a quantitative measure of the relative level of the two or more target nucleotide sequences in the sample.

7. (Amended) A method according to claim 6, wherein one of the oligonucleotide probes in each set [contains] comprises a restriction site, said method further comprising:

restriction digesting the extension products at the restriction site[s] to produce [labelled] extension product fragments, wherein the restriction site is positioned in each of the oligonucleotide probe sets to produce an extension product fragment with a unique length so that it can be distinguished from other nucleic acids in the polymerase chain reaction mixture after said restriction digesting; and

separating the extension product fragments by size or electrophoretic mobility, wherein said [distinguishing] detecting is carried out by size differences in the [labeled] extension product fragments.

8. (Amended) A method according to claim 6, wherein oligonucleotide probe sets in the same group [contain] comprise the same 5' upstream primer-specific portion and the same 3' downstream primer-specific portion, and the ligation product sequences of oligonucleotide probes in [a] each particular set have a unique length product so that they can be distinguished from other nucleic acids in the polymerase chain reaction mixture, said method further comprising:

separating the extension products by size or electrophoretic mobility, wherein said detecting [and said distinguishing are] is carried out by size differences in the [labeled] extension products.

9. (Amended) A method according to claim 6, wherein the ligation product sequences of oligonucleotide probes in [a] each particular set [contain] comprise

unique sequences [across the ligation junction] so that they can be distinguished from other nucleic acids in the polymerase chain reaction mixture, said method further comprising:

providing a solid support with different capture oligonucleotides immobilized at different particular sites, wherein the capture oligonucleotides have nucleotide sequences complementary to the unique nucleotide sequences [across the ligation junctions] of given probe sets;

contacting the polymerase chain reaction mixture, after said subjecting it to one or more polymerase chain reaction cycles, with the solid support under conditions effective to hybridize the extension products to the capture oligonucleotides in a base-specific manner[, thereby capturing the extension products on the solid support at the site with the complementary capture oligonucleotide, wherein said]; and

detecting [indicates] the presence of extension products captured [using the unique nucleotide sequence portions across the ligation junction and immobilized to the solid support] at particular sites.

10. (Amended) A method according to claim 1, wherein one or both oligonucleotide probes in [a] each particular set [have] comprise blocking groups at their non-ligating ends with blocking group rendering the ligation product sequence of the oligonucleotide probes in a particular set substantially resistant to exonuclease digestion, said method further comprising:

subjecting the ligase detection reaction mixture to exonuclease digestion after said subjecting the ligase detection reaction mixture to one or more ligase detection reaction cycles[, wherein exonuclease substantially destroys oligonucleotide probes which are not blocked, does not destroy a substantial portion of the ligation products, and substantially reduces the presence of original target nucleotide sequences] and

inactivating the exonuclease[, wherein said subjecting to exonuclease digestion reduces formation of ligation independent extension products during said subjecting the polymerase chain reaction mixture to one or more polymerase chain reaction cycles].